MGZ
Medical Genetics Center

Clinician Information

PRIMARY ARRHYTHMIA SYNDROMES

The most common primary arrhythmia syndromes (cardiac ion channel diseases) include:

- Long QT syndrome (1:2000-1:5000)
- Brugada syndrome (1:5000-1:10,000)
- Catecholaminergic polymorphic ventricular tachycardia (1:10,000)
- Short QT syndrome (very rare)

MAIN SYMPTOMS OF PRIMARY ARRHYTHMIA SYNDROMES

Primary arrhythmia syndromes are characterized by a disturbance of stimulus transmission in the cardiac muscle cell in a structurally normal heart. For people who experience signs and symptoms, the most common include:

- Dizziness
- Loss of consciousness (syncope)
- Ventricular tachycardia
- Sudden cardiac death

DIAGNOSTIC STRATEGY

The diagnosis and management of patients with primary inherited arrhythmias require a specialized multidisciplinary approach. Genetic testing has an important role in supporting a diagnosis of a primary arrhythmia disorder. Early diagnosis, appropriate behaviors and adequate therapy can reduce the risk of sudden cardiac death. A detailed patient and family medical history should always be included. Secondary causes due to medication and electrolyte disturbances need to be excluded.

Basic cardiac diagnostic testing: 12-lead resting electrocardiogram (ECG), exercise ECG, long-term ECG monitoring, echocardiography

LONG QT SYNDROME (LQTS)

Abnormalities in the ECG: **Prolonged QT intervals** (frequency-corrected QT intervals (QTc) according to Bazett´s formula, QTc = QT /√ RR, **altered T-wave morphology, 20% of these patients do not have prolonged QTc intervals; LQTS1:** broad-based T-wave with relatively high amplitude; **LQTS2:** notching of the T-wave; **LQTS3:** relatively long ST segment, narrow-based T-wave and relatively low amplitude.

LQTS type 1 LQTS type 2 LQTS type 3

Age of onset: usually childhood or young adulthood

Genes: 75% of clinically proven cases carry sequence variations in genes of repolarizing potassium channels *(KCNQ1, KCNH2, KCNE1, KCNE2)* and a sodium channel *(SCN5A)*.

- **Jervell Lange-Nielsen syndrome** with inner ear hearing loss, autosomal recessive inheritance *(KCNQ1)*
- **Romano-Ward syndrome** without inner ear involvement, autosomal dominant inheritance *(KCNQ1)*

Schwartz score (calculating the probability of Long QT syndrome):
≤1.5: low, 1.5-3: medium, ≥3: very high

Abnormalities in the ECG		Patient Medical History	
QTc ≥480	3	Syncope, stress-induced	2
QTc 460-479	2	Syncope, other cause	1
QTc 450-459 (men)	1	Inner ear hearing loss (congenital)	0.5
QTc ≥480 after stress test	1		
T-wave alternans	1	**Family Medical History**	
T-wave notches	1	Family member with LQTS	1
Low heart rate	0.5	Unexplained sudden cardiac death <30 years	0.5
Torsade de Pointes	2		

Confirmation of diagnosis if one of the following criteria is met:

- QTc ≥480 ms in repeated 12-lead ECG
- LQTS risk score (Schwartz score) >3
- Pathogenic variant in a LQTS gene, regardless of the QT duration

SHORT QT SYNDROME (SQTS)

Abnormalities in the ECG: short QT interval <330 ms, high peak T-wave

Age of onset: usually ages 20-40

Genes: *KCNH2, KCNQ1* and *KCNJ2*, overactive potassium channels with shortened action potential, predominantly autosomal dominant inheritance

Calculating the probability of Short QT syndrome:
≤2: low, 3: medium, ≥4: very high

Abnormalities in the ECG	
QTc <370 ms	1
QTc <350 ms	2
QTc <330 ms	3
T-wave <120 ms (J-point until the peak)	1

Patient Medical History#	
Syncope, unclear	1
Polymorphic ventricular tachycardia	2
Ventricular fibrillation	1
Atrial fibrillation	1
Survived sudden cardiac arrest	2

Genotype#	
Pathogenic variant (SQTS gene)	2
Unclear sequence variant (SQTS gene)	1

Family Medical History#	
1st or 2nd degree relative with SQTS	2
1st or 2nd degree relative with PHT (with normal autopsy)	1
Sudden infant death	1

Only evaluated by at least one additional point due to ECG changes

BRUGADA SYNDROME (BrS)

Abnormalities in the ECG: **ECG type 1:** Cove-shaped ST elevation in right precordial leads with J wave or ST elevation of ≥2 mV at its peak followed by a negative T wave with little or no isoelectric interval in more than one right precordial leads V1 through V3. **ECG type 2:** The ST segments also have a high take-off but the J amplitude of ≥2 mV gives rise to a gradually descending ST elevation remaining ≥1 mV above the baseline followed by a positive or biphasic T wave that results in a saddleback configuration. **ECG type 3**: Right precordial ST elevation of <1 mV of saddleback type or coved type.

ECG type 1 ECG type 2 ECG type 3

Age of onset: ages 30-50, often inconspicuous ECG in childhood

Genes: 20%-30% variants in the SCN5A gene (alpha subunit of the sodium channel (BrS type 1) with reduced ion channel activity), other genes less common, predominantly autosomal dominant inheritance

Confirmation of diagnosis: The diagnosis for Brugada syndrome can only be determined by using **a type 1 ECG** (ST segment elevation ≥2 mm in ≥1 derivation of the right chest wall leads V1 and/or V2, which can be positioned in the 2nd, 3rd or 4th intercostal space), so that the type 2/3 ECG is only useful for determining a diagnosis if it can be converted into a type 1 ECG by inducing it with a sodium channel blocker (e.g. Ajmaline).

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

Abnormalities in the ECG: adrenergic triggered **bidirectional or polymorphic ventricular tachycardia**

Age of onset: usually ages 7-12

Genes: 60%-70% variants in the **ryanodine type 2 receptor gene** ***(RYR2)***, the Ca^{2+}-releasing channel of the sarcoplasmic reticulum, 3%-5% variants in the calsequestrin 2 gene ***(CASQ2)***, **rare in** *TRDN*, *CALM1*, **autosomal dominant and recessive inheritance**

CLINICAL UTILITY / CLINICAL VALUE OF HUMAN GENETIC DIAGNOSTIC TESTING

Individuals clinically diagnosed with **LQTS** or **CPVT** (class I of recommendation), **Brugada syndrome** (class IIa of recommendation), or **SQTS** (class IIb of recommendation).

Predictive genetic diagnosis with a known mutation in the family (class I of recommendation)

RISK ASSESSMENT AND MANAGEMENT OF PRIMARY ARRHYTHMIA SYNDROMES

Specific precautions depending on the genotype:

- Avoidance of competitive sports is recommended.
- Avoidance of genotype-specific triggers for arrhythmias (strenuous swimming, especially in LQTS1, and exposure to loud noises in LQTS2 patients).
- Avoidance of QT-prolonging drugs. (www.crediblemeds.org)
- Avoidance of drugs that may induce ST-segment elevation in right precordial leads. (www.brugadadrugs.org)
- Correction of electrolyte abnormalities that may occur during diarrhea, vomiting or metabolic conditions (LQTS).
- Prompt treatment of any fever with antipyretic drugs (LQTS and BrS).

* European Society of Cardiology (ESC) guidelines define competitive sports as regular recreational or professional participation in athletic training and public competitions.

TREATMENT RECOMMENDATIONS (ACCORDING TO THE EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES)

Beta-blockers
Beta-blockers are recommended in patients with a clinical diagnosis of LQTS or CPVT (class I of recommendation). Beta-blockers should be considered in carriers of a causative LQTS or CPVT mutation (class IIa of recommendation).

Implantable cardioverter defibrillator (ICD) with the use of beta-blockers is recommended in LQTS and CPVT patients who experience cardiac arrest, (class I of recommendation). ICD shall be considered in LQTS or CPVT when ventricular tachycardia (VT) and/or syncope occur despite the patient following the precautions and receiving adequate beta-blocker treatment (class IIa of recommendation). ICD implantation is recommended in patients with a diagnosis of BrS or SQTS who are survivors of an aborted cardiac arrest and/or have documented spontaneous sustained VT (class I of recommendation). ICD implantation should be considered in patients with a spontaneous diagnostic type I ECG pattern and history of syncope (class IIa of recommendation).

Left cardiac sympathetic denervation (LCSD) is an option for therapy-resistant LQTS (class IIa of recommendation) and CPVT (class IIb of recommendation) and in patients who are intolerant or have a contraindication to beta-blockers.

PROFILE OF PRIMARY ARRHYTHMIA SYNDROMES

Main Symptoms

Structurally normal heart, dizziness, syncope, life-threatening arrhythmias

Genetic Causes

Genetic alterations in genes encoding cardiac ion channels or associated regulatory proteins

Frequency

Long QT 1:2000, others less common

Inheritance

Mostly dominant, rarely recessive

Age of Onset

Childhood to adulthood

Development

Sudden cardiac death in childhood, adolescence, or adulthood to clinically symptom-free carriers

LITERATURE

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IMAGE REFERENCE

The images have been modified by MGZ – Medical Genetics Center.

Figure 1 is based on: Author: ExCard Research GmbH | Title: LQT Subforms
URL: https://www.fokus-ekg.de/inhalt-von-a-z/famili%C3%A4re-arrhythmiesyndrome/langes-qt-syndrom/
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Figure 2 is based on: Author: ExCard Research GmbH | Title: Brugada ECG Image
URL: https://www.fokus-ekg.de/inhalt-von-a-z/brugada-syndrom/
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